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CONCISE DEFINITIVE REVIEW

Bram Rochwerg, MD, MSc (Epi), FRCPC, Series Editor

The Effective Management of Shock: Moving From Physiology to Guidelines to Personalized Medicine

Michael R. Pinsky, MD, Dr hc, MCCM

ABSTRACT: Central to managing critically ill patients is the identification of the etiology of cardiorespiratory insufficiency (i.e., shock), early appropriate targeted therapies to support the cardiorespiratory system to sustain adequate blood flow and oxygen to the tissues, plus specific treatments to reverse the cause of shock. Over the past 40 years, numerous advances in our understanding of shock, its severity, and its response to therapies, along with more specific and insightful monitoring approaches, have been developed. This perspective summarizes some aspects of that progress. We have come a long way, but we need to understand three things. First, that once organ injury has occurred all that our treatments can do is mitigate further injury, not reverse it. If initial aggressive resurrection efforts cannot restore organ function, then their actions often cause only iatrogenic injury. Second, existing advanced monitoring devices, no matter how insightful their data, will not improve patient outcomes unless coupled to a treatment that itself improves outcomes. Finally, all our advances over these years have underscored the fundamental need for having a thoughtful and observant bedside clinician cognizant of the pathophysiologic underpinnings of disease and its care who titrates care based on the patient's individual response.

KEYWORDS: historical review; monitoring; physiology; resuscitation; tissue perfusion

John Collins Warren described shock as a "momentary pause in the act of death." This remains true today if the presence of shock is missed or treatment delayed (1). However, nature never envisioned that healthcare or medicines existed to fend off shock. Evolutionary forces created adaptive physiologic responses to insult that presume that they are dealing with either hypovolemia or sepsis. And that they are dealing with it alone. With the advent of potentially life-saving therapies, it became necessary to quickly identify which patients were in shock, its cause and how they responded to therapies aimed at both supporting cardiorespiratory status and reversing the primary shock etiology. These goals required more accurate, ongoing and insightful assessments of shock's complex pathophysiology and methods to support bodily functions in the setting of organ failure. We have witnessed extraordinary changes in our understanding of cardiorespiratory insufficiency and its offspring, multiple organ failure (2). Along the way, we also realized that the goal of resuscitation is not to restore normal physiologic "numbers" but to restore adequate tissue perfusion and metabolism to allow the body to recover while minimizing iatrogenic injuries.

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PHYSIOLOGIC CLASSIFICATION OF SHOCK

Some of our earliest understanding of shock physiology came from large animal models of profound hemorrhagic shock by Wiggers (3) in 1942, Richards (4) in 1954, and for distributive shock by MacLean and Weil (5) in 1956. In 1958, Weil and Shubin (6) opened a four-bed "shock ward" in LA County Hospital. In the late 1960s, they created a simplified nosology of shock that could rapidly stratify shock etiologies into four broad categories: cardiogenic, obstructive, hypovolemic, and distributive. These groupings could be identified by bedside inspection and hemodynamic monitoring. By definition, all forms of shock are associated with evidence of end-organ dysfunction, presumed be due to hypoperfusion with altered sensorium, ileus, hyperlacticemia, decreased urine output, increased tissue P_{CO_2}, and increased arteriovenous oxygen content differences. Reactive increased sympathetic tone caused tachycardia, diaphoresis, skin mottling, and decreased capillary refill time (CRT).

PHYSIOLOGY-BASED MANAGEMENT

In the mid-1970s, the ballon floatation pulmonary artery catheter (PAC) became widely available. From this monitoring platform associated with measures of arterial pressure and blood gas analysis, defining the physiologic signatures of shock had its heyday (7). The logic of this approach was simple. If a specific cause of shock that was treatable could be diagnosed, then appropriate treatment could be given, and the response followed until recovery. Treatments were usually focused on restoring "normal" physiologic values independent of the underlying disease, which were themselves treated separately. This era generates for the present the clinical scientific foundation of cardiopulmonary physiology and the determinants of blood flow (8).

Although mortality from shock, especially traumatic shock, decreased, management consistency was not sustained. Acute kidney injury and acute lung injury often were created or persisted. Marked practice pattern variations in care were common (9). Major national educational programs were developed to create a minimal level of clinical competence in both understanding the data and their translation into actionable events. Several barriers to the effective realization of this educational approach were obvious. First, individual patients vary widely in their expression of disease, existing comorbidities, cardiorespiratory reserve, and response to therapy. Second, in many patients, shock cannot be cleanly separated into one of four groups.

With the hope of treating shock as inadequate tissue blood flow, retrospective analyses of large clinical databases documented that high blood lactate and low systemic oxygen delivery (Do_2) were strong predictors of death (10). There was weaker evidence that if Do_2 spontaneously increased mortality was less than in those who did not. This threshold Do_2 was coined "survival levels" of Do_2 (11). A mass movement of aggressive fluid resuscitation and vasoactive drug therapy followed. Subsequent prospective studies demonstrated not only no survival advantage of targeting "survivor Do_2 levels" (12), but a treatment-associated higher mortality (13). Finally, Connors et al (14) in a subgroup analysis of study of quality of life on terminally ill patients demonstrated that the presence of a PAC increased mortality. Presumably, those were the patients subjected to survival Do_2 levels protocols, but that association was unfortunately never assessed in their report. Additional prospective studies did not demonstrate harm in PAC use but did not show a benefit either (15, 16). Regrettably, what is often forgotten is that no monitoring device, no matter how insightful and accurate its data, will improve patient-centered outcomes unless such treatment themselves improve outcome (17). No specific therapies shown to improve outcome were linked to PAC-derived diagnosis; thus, increasing Do_2 alone would not be expected to impact outcomes. Interestingly, Gutierrez et al (18) showed that if critically ill patients without evidence of gut ischemia were treated to sustain gut blood flow, their mortality was less than those with preexisting ischemia no matter what the treatment. Thus, preventing ischemia improves outcomes, whereas treatment after the fact is less effective.

BUILDING BETTER MOUSE TRAPS

In parallel with the greater appreciation of the complex inter-related physiologic network defining shock, many new minimally invasive monitoring devices became available. While the patient in shock in an ICU in the 1980s would likely have both PAC and arterial catheters, the lack of documented benefit caused a rapid decrease in PAC. To replace these invasive monitors,

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echocardiography became more prevalent along with minimally invasive CO monitoring devices (19). Yet with all these new parameters, no specific treatments guided by these new parameters were shown to alter outcome.

GOAL-DIRECTED THERAPY

Although in practice all therapy should be goal-directed, the phrase "early goal-directed therapy" (EGDT) in septic shock resuscitation became a call to arms in 2005. Rivers et al (20) observed that in their emergency department (ED), once a patient was identified as having septic shock, cultured and given antibiotics and a large fluid bolus, the subsequent admitting hospital service often did not see the patients for hours because of inpatient demands on their time. Their response was to create a small ED ICU, like Weil's Shock Ward 40 years earlier. The logic was simple: if the patient is in shock, get them out of shock as soon as possible. EGDT treated low Do_2, with blood transfusion to treat a low central venous oxygen saturation ($Scvo_2$) and target minimal mean arterial pressure (MAP) and CO values with fluids and vasopressors. The resuscitation protocol used had its weaknesses, but it was better than grossly delayed care (20). Their small single-center study lit a fire in acute care medicine.

At about the same time two other important studies came out that focused on the generic treatment of shock processes. Van den Berghe et al (21) while studying the impact of high-dose insulin on homeostasis as an adjuvant treatment of high-risk surgical patients showed that the associated necessary tight glucose control improved survival. Also, Bernard et al (22) published the large multicenter clinical trial of recombinant human activated protein C (APC) as immune therapy for septic shock, showing a decreased length of stay in a subgroup of septic patients but no effect on survival. It seemed logical to combine EGDT early blood transfusion, monitoring $Scvo_2$ with both tight glucose control, and APC in the management of septic shock patients. Surprisingly, to the industry that had sponsored the APC trial, subsequent use of APC was modest. To help get faster adoption and hopefully save lives, a new blue-ribbon international committee, completely funded by industry, performed a literature review of all known clinical trials in the treatment of sepsis, reporting on which treatments had been shown to be effective (23). This was an exciting time because even though the initial studies had not been duplicated elsewhere, the proposed approach seemed logical. Their Surviving Sepsis Guidelines (SSG) became the rallying point. They proposed the immediate use of antibiotics and source control, rapid initial large-bolus fluid infusion followed by vasopressors but avoidance of both survivor levels of Do_2 and high-dose steroids, both of which were shown to increase mortality. To monitor such patients, they recommended invasive monitoring of $Scvo_2$ to drive transfusion, tight glucose control, and APC in high-risk patients with evidence of organ failure. A massive industry-sponsored international education program followed the initial SSG publication. Regrettably, three large randomized clinical trials (ProCESS [24], ARISE, ProMIse) subsequently showed that most of the elements of the EGDT bundles were not as important as early and continual resuscitation (24). Similarly, neither tight glucose control (25) nor recombinant human APC (26) was shown to be effective in follow-on clinical trials. As a side note, the failure to document improved outcomes from EGDT was probably because, following its initial publication, close titration of care of septic shock patients became the norm in EDs and ICUs. This underscores the need for careful duplication of exciting initial findings and linking them to clear pathophysiologic mechanisms before widespread endorsement.

However, physiologic support still seemed like a reasonable target, but to what end? Over-resuscitation with fluids commonly occurred and increased mortality (27) and was strongly associated with acute kidney injury (28), whereas prolonged vasopressor use for greater than 6 hours was independently associated with increased mortality (29). Similarly, the amount of fluids, independent of their response (CLASSIC, CLOVERS), does not seem to matter (30, 31). It seems logical that treatment should be effective, but that was not the case in the above multicenter studies. It was clear that overzealous iatrogenic resuscitation was often detrimental to beneficial outcomes from shock, and under-resuscitation was harmful if fluids could improve perfusion, minimizing at-risk tissue injury.

Today, the SSG reflects thoughtful evidence-based guidelines linked to realistic approaches. However, a major unanticipated consequence of the SSG promulgation was to make them into mandatory treatment protocols defining institutional quality of care,

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occasionally linked with nonresponsive financial punishments. Time-dependent relevance of SSG has demonstrated that the early administration of appropriate antibiotics as soon as possible has a strong survival signal (32). This seems logical because the cause of sepsis is infection, and if appropriate antibiotics are available, they should be beneficial. What has not proven is the mandated initial 30 mL/kg crystalloid infusion within the first 3-hour bundle. Indeed, Guarracino et al (33) showed that slightly more than half the septic shock patients presenting to an ED increased their CO in response to an initial 30 mL/kg crystalloid infusion. In the rest of the patient iatrogenic fluid overload occurred. There then arose a chorus of objections to such a "one-size-fits-all" approach to the management of septic shock (34). In their defense, SSG modified their 30 mL/kg crystalloid fluid resuscitation recommendation from strong to weak (35).

BACK TO THE BASICS: APPLIED PHYSIOLOGY

Interestingly, at the same time, the initial above clinical trials of improved outcomes were being reported, we documented that dynamic parameters of volume responsiveness could accurately predict which critically ill patients on mechanical ventilation would increase their CO in response to a fluid challenge (volume responsive) and which would not (nonresponsive) (36). Similarly, it could identify which patients with acute respiratory distress syndrome would tolerate a step increase in positive end-expiratory pressure (PEEP) without a fall in CO and which would deteriorate (37). In both studies, ventilator-induced cyclic changes in arterial pulse pressure, termed pulse pressure variation (PPV), defined a common threshold of 13% above which patients were volume responsive and PEEP intolerant. PPV could be easily assessed at the bedside. Stroke volume variation (SVV) assessed by minimally invasive monitoring soon followed as a volume responsiveness parameter (38). Although PPV and SVV have limitations, modifications of those tidal volume maneuvers and using changes in CO in response to passive leg raising have received more acceptance (39). These functional hemodynamic parameters can guide fluid resuscitation while avoiding giving fluids to those not responsive (40). Indeed, Guarracino et al (33) showed that the cardiac output response to an initial fluid bolus in septic patients was predictable from the PPV and SVV values observed before the bolus. The latest SSG recommends the use of such dynamic parameters to guide fluid resuscitation (35).

But restoring CO alone may not increase MAP nor result in increased tissue perfusion. Since shock is an inadequate tissue perfusion, the primary cardiovascular focus should be on restoring appropriate tissue blood flow. The determinants of tissue blood flow include the metabolic demands of the tissue, the driving pressure for blood flow, the resistance to that pressure, and the tissue or venous backpressure to that flow (41). Tissue blood flow is regulated by local metabolic demand under normal conditions, not by CO or MAP. By decreasing the feeding of small arteries and arterioles, the vasomotor tone without any change in MAP. Local blood flow autoregulation is a fundamental aspect of effective circulation. Without autoregulation CO would need to be at least ten times higher to support basal metabolic demands. The mechanism by which autoregulation functions is by varying their inflow arteriole vasomotor tone, at which loci arterial pressure is rapidly decreasing owing to flow-induced resistance, such that vasomotor tone exceeds vascular pressure causing these feeding vessels to spontaneously collapse, throttling flow. The luminal pressure at those sites is called the critical closing pressure (Pcc). For effective tissue blood flow, at a minimum one needs a high enough MAP as the input pressure and a Pcc higher than the receiving organs tissue and capillary pressures so that changes in changes in Pcc will result in changes in blood inflow. Large epidemiology studies of critically ill patients demonstrate that as MAP increases from 65 to 85 mm Hg, mortality and acute kidney injury proportionally decrease (42). Prospective clinical studies targeting a minimal MAP during sepsis resuscitation support this approach (43). Indeed, in septic patients with hepatic cirrhosis who have intrinsic vasoplegia, increasing MAP with vasopressors improves renal blood flow (44). However, a larger multicenter study of septic shock patients did not find a mortality difference between 65 and 75 and 80–85 mm Hg MAP targets (45). Still, their low blood pressure group had a MAP in the 70–75 mm Hg range, not 65 mm Hg. Recently, Andrei et al (46) demonstrated in vasoplegic cardiac surgery patients that increasing MAP from 60 to 85 mm Hg using norepinephrine only improved microcirculatory flow in half the patients, those whose

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Pcc also increased to values high enough to create a pressure difference between Pcc and the microcirculation. This vascular pressure difference is referred to as a vascular waterfall (46). Thus, increasing MAP alone without also reestablishing a vascular waterfall may not be effective at reestablishing tissue blood flow autoregulation. In a retrospective analysis of large postoperative cardiac surgery database, threshold MAP values of 74 mm Hg and tissue perfusion pressure (MAP–Pcc) of 35 mm Hg were shown to be highly correlated risk of mortality, hospital length of stay, and peak blood lactate levels (47). Importantly, hypotension alone abolishes autoregulation even if normal vascular responsiveness is present because there is no driving pressure. Thus, early use of vasopressors in septic patients is associated with a reduction to total fluids administered and less time in a hypotensive state (43). CRT may be a simple bedside method of assessing tissue perfusion (48). Recently, a multicenter, prospective clinical trial compared SSG to a targeted tissue perfusion goal using a MAP between 50 and 60 mm Hg in 97 severe septic patients in each arm. Measures of restoration of adequate tissue blood flow were CRT, lactate, and skin temperature. Targeting tissue perfusion at a lower MAP was noninferior to SSG-based therapy in terms of 30-day survival and serious adverse events (49). But noninferior is not improved care.

Delayed vasopressor use increases mortality is septic shock (50) The MAP response to increasing CO in vasoplegic states can be predicted by the PPV/SVV ratio, called dynamic arterial elastance (Ea_{dyn}). If greater than 1, then MAP should increase (51). Similarly, norepinephrine weaning based on an adequate MAP can be safely done if Ea_{dyn} is greater than 1 (52) and earlier norepinephrine weaning reduces the incidence of acute kidney injury (53). Knowing volume responsiveness and Ea_{dyn} lends itself to closed-loop autonomous diagnosis and resuscitation of hypovolemic and septic shock (54). However, even these powerful functional hemodynamic principles can only serve as broad fencepost defining goals of resuscitation. What is needed is a personalized physiologically based resuscitation strategy.

PRECISE RESUSCITATION FOR SHOCK

But as the EGDT studies illustrated, if resuscitation cannot restore tissue blood flow before ischemic or toxic injury ensues in shock patients, then the primary effects will be iatrogenic harm. The assumption of resuscitation is that by increasing MAP and CO, tissue blood flow will also increase. In early sepsis (< 6 hr) and acute trauma, if treated immediately, that is the case. But once organ failure ensues, these same resuscitative efforts often are not associated with increased microcirculatory flow or end-organ function. Sublingual microcirculation in such patients, whose microcirculatory flow was diminished increased it with vasodilators (55). Thus, the microvasculature is reactive, just not allowing increased flow.

All these new guidelines and management principles ignore one basic reality. We cannot treat established acute organ failure by any presently known treatment. We can only support the body cardiorespiratory system while minimizing iatrogenesis, allowing the body to recover. The body behaves as if it is in this battle alone. And its only goal is to survive. Presumably, the organs decrease their mitochondrial function through metabolic reprogramming as a primordial survival mechanism (56, 57). Importantly, when patients who died with sepsis with anuria and elevated serum creatinine were autopsied, minimal renal injury was seen (58). The outward result is multiple system organ failure without tissue necrosis or apoptosis.

Recently, Hernandez et al (59) performed a large, prospective, multicenter, randomized clinical trial of resuscitation of patients in the early phase of septic shock based on improving tissue perfusion by personalized blood pressure and flow targets as compared with SSG values. They showed that such personalized resuscitation, using normalization of CRT and arterial pulse pressure as endpoints of resuscitation, required slightly lower MAP values and better composite outcomes. The principles of their protocol are also part of the European Society of Intensive Care Medicine report "Guidelines on Circulatory Shock and Hemodynamic Monitoring, 2025" (60).

ARTIFICIAL INTELLIGENCE TO REACH PERSONALIZED PRECISE RESUSCITATION

Plumbing massive critically ill patient databases using artificial intelligence tools has identified dynamic

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individualized clinical decision-support that in silico improved outcomes from shock (61). Our group has focused on identifying when a patient reaches sufficiency during resuscitation, so as to limit therapy (62). These decision-support models need to be trialed but hold great promise for personalized precise resuscitation.

CONCLUSIONS

It has been an amazing 40 years of medical progress and evolving insights into shock pathophysiology. But through it all, having a thoughtful bedside clinician cognizant of the pathophysiologic underpinnings of disease and its care who titrates care based on the patient's individual response represents, for now, the gold standard for best practice.

Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

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For information regarding this article, E-mail: pinsky@pitt.edu

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